FDA's Focus on Laboratory Data Integrity – Part 1

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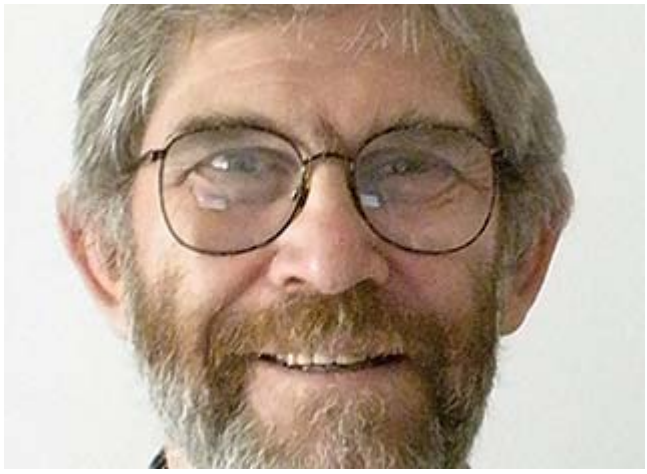
by R.D. McDowall



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A look at this current emphasis and a few problems inspectors have identified

The integrity of data generated by a regulated laboratory can make or break a regulatory inspection or audit. This paper looks at what is required for data integrity from the basis of the GMP regulations. It presents examples of non-compliances found in warning letters and a regulatory action from the U.S. Food and Drug Administraqtion (FDA). It only requires a single adverse non-compliance to cast a shadow over ALL work undertaken by a regulated laboratory. In this first installment of a two-part article, we will look at the background to the current FDA emphasis on data integrity and some of the problems that their inspectors have found when visiting companies.

To begin a discussion about laboratory data integrity, it is necessary to start from basics, in this case the definition of integrity as being the quality or condition of being whole or undivided; completeness.[1] In the context of laboratory data integrity within a GMP environment, this can be defined as: generating, transforming, maintaining and assuring the accuracy, completeness and consistency of data over its entire life cycle in compliance with applicable regulations. This definition is consistent with one of the principles of ICH 10 on Pharmaceutical Quality Systems,[2] which discusses life cycle processes. Therefore, data and the accompanying integrity attribute have such a life cycle, which is represented in the definition above.

GMP Regulatory Requirements for Data Integrity

Derived from the laboratory data integrity definition and the applicable 21 CFR 211 GMP regulations3 are some of the following points:

- Instruments must be qualified and fit for purpose [§211.160(b), §211.63]
- Software must be validated [§211.63]
- Any calculations used must be verified [§211.68(b)]
- Data generated in an analysis must be backed up [§211.68(b)]
- Reagents and reference solutions are prepared correctly with appropriate records [§211.194(c)]
- Methods used must be documented and approved [§211.160(a)]
- Methods must be verified under actual conditions of use [§211.194(a)(2)]
- Data generated and transformed must meet the criterion of scientific soundness [§211.160(a)]
- Test data must be accurate and complete and follow procedures [§211.194(a)]
- Data and the reportable value must be checked by a second individual to ensure accuracy, completeness and conformance with procedures [§211.194(a)(8)]

The key issue when it comes to release testing is the requirement stated in 211.194(a)[3] for complete data: A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component ……, or drug product, and lot tested. There then follows a list of seven sub clauses specifying in more detail what is required from the QC laboratory.

The bullet list above is generated directly from the GMP regulations,[3] before we consider the interaction with 21 CFR 11 for electronic records and signatures4 or the respective general chapters from the United States Pharmacopoeia[5] for instrument techniques and method verification. The last two references do not change the list above, but certain aspects are reinforced when using a computerized system to automate the process, e.g. the computerized system used to generate data can be used either in a hybrid or completely electronic mode,[4] or it controls the way chromatographic tests should be conducted.[5]

Barriers to Complete Data

However, data integrity and the lack of complete data over the record retention period can be compromised in a number of ways, such as:

- Human errors when data is entered by mistake (an uncorrected fat finger moment), stupidity (not being aware of regulatory requirements or poor training) or wilfully (falsification or fraud with the intent to deceive)
- Selection of good or passing results to the exclusion of those that are poor or failing
- Unauthorized changes to data made post-acquisition
- Errors that occur when data is transmitted from one computer to another
- Changes to data through software bugs or malware of which the user is not aware
- Hardware malfunctions, such as disk crashes

- Changes in technology, where one item is replaced when it becomes obsolete or no longer supported, making old records unreadable or inaccessible

Compliance Program Guide 346.832

Over the past 10 years, FDA inspectors have uncovered many cases of data falsification in the laboratory. This may range from copying an IR spectrum from a passing batch of material to an untested batch[6] to the Able Laboratories fraud case.[7,8] One of the problems with the Able Laboratories case was that the FDA had carried out a number of pre-approval inspections (PAIs) prior to the for-cause inspection without any serious observations. The reason is that the inspectors had focused on the signed paper printouts from the chromatography data system (CDS) rather than looking at the original electronic records. However, it was the audit trail within the CDS that showed to the inspectors carrying out the inspection in 2005 what changes had been made and who made them. In addition, there was the Ranbaxy data falsification case, which will be discussed later in this article.

In response to the failure to detect the falsification of records at Able Laboratories and to focus inspectors when conducting PAIs, the FDA has taken two steps to overcome it. The first is the publication in 2010 of Compliance Program Guide (CPG) 7346.832, which became effective in May 2012 on Pre-Approval Inspections.9 The second is that all inspectors have had data integrity training that will be discussed later in this article.

The CPG9 has three primary objectives, which are:

1. Readiness for Commercial
2. Manufacturing
3. Conformance to Application
4. Data Integrity Audit

Under the CPG Objective 2, the inspector needs to verify, among other things, that the analytical methods are consistent with descriptions contained in the CMC section of the application for key batches of API and product produced. The inspector will focus on comparing the description of the methods contained in the application with those in actual use to see if there are significant variations from the method filed. In addition, they will look at the validation data and report of each of the methods to look for consistency throughout the validation and use of the method. Finally, the use of the method will be reviewed in operational use, including out-of-specification results and deviations to see if it is reliable or not.

However, the detailed inspection in the laboratory comes under Objective 3 for the data integrity audit. Here, the inspector will look at both the hardcopy and electronic records to verify that the data submitted in the application is both complete and accurate and to ensure that inconvenient data have not been ignored and omitted from the application. The CPG suggests that data on finished product stability, dissolution, content uniformity and API impurity are good candidates for the data integrity audit.

During the inspection, compare raw data, hardcopy or electronic, such as chromatograms, spectrograms, laboratory analyst notebooks, and additional information from the laboratory with summary data filed in the CMC section. Raw data files should support a conclusion that the data/information in the application is complete and enables an objective analysis by reflecting the full range of data/information about the component or finished product known to the establishment.

Examples of a lack of contextual integrity include the failure by the applicant to scientifically justify non-submission of relevant data, such as aberrant test results or absences in a submitted chromatographic sequence, suggesting that the application does not fully or accurately represent the components, process, and finished product.[9]

According to the FDA, the following are possible data integrity problems in the laboratory that have been observed in the past:

- Alteration of raw, original data and records (e.g., the use of correction fluid)
- Multiple analyses of assay with the same sample without adequate justification
- Manipulation of a poorly defined analytical procedure and associated data analysis in order to obtain passing results
- Backdating stability test results to meet the required commitments
- Creating acceptable test results without performing the test
- Using test results from previous batches to substitute testing for another batch

The overall aim of the data integrity audit under objective 3 is to assure the FDA reviewers of the drug application that they can rely on the data contained in the submission as accurate and complete. However, if data integrity discrepancies are observed, the FDA requires the personnel responsible to be identified, which could be an example of your name going up in lights, but for the wrong reasons.

Paper or Electronic Records?

The pharmaceutical industry is very conservative and, as such, is very slow to change. Many laboratories, either due to this conservative nature or dinosaurs in quality assurance, continue to define the primary record / source data / raw data as paper even when it is generated by a computer, such as a chromatography data system. This debate has gone on since the 1980s and the widespread use of computers in regulated laboratories; however, the debate is ended, as the FDA has issued a statement on their Web site that finishes the discussion once and for all.

Around the same time that the FDA issued CPG 7346.832, the agency issued more detailed guidance aimed at chromatography data systems used in quality control laboratories working to GMP. This is available on the FDA Web site under the snappy title of Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Records and Reports.[10] Item 3 is a question concerning the interpretation of the GMP predicate rule3 and the applicability of Part 114 to chromatographic data systems. The Web page poses the question "How do the Part 11 regulations and predicate rule requirements for GMP apply to the electronic records created by computerized laboratory systems and the associated printed chromatograms that are used in drug manufacturing and testing?" Although the FDA's answer to the question is based on chromatography data systems, it is applicable to all laboratory computerized systems. The FDA starts by stating that "Some in industry misinterpret lines 164 to 171 from the Part 11 Guidance11 to mean that in all cases paper printouts of electronic records satisfy predicate rule requirements in 21 CFR Part 211."

Therefore, the key to the debate is, what do the predicate rules state and how should they be interpreted for a computerized laboratory system, such as a chromatography data system? The FDA then comments that for a CDS used in a quality control laboratory, this involves user inputs, outputs, audit trails, etcetera, and that there are two clauses from the GMP regulations applicable for the interpretation of paper versus electronic records debate. These are §211.68 and §211.180(d).[3]

21 CFR 211.180(d) states that manufacturing records must be retained "either as original records or true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records." This clause shows how old the US GMP is, because it mentions microfilm and microfiche and this part of the regulation has not been updated since it was issued 1978.

21 CFR 211.68 further states that: "Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained."

The FDA states10 that paper printouts of chromatograms fail to be a true copy under 211.180(d) of the electronic records used to create the paper chromatogram. Furthermore, it is not a complete and exact copy of the electronic records as required by 21 CFR 211.68, as there is typically not the injection sequence, various instrument, acquisition or processing methods and certainly not the linked audit trail entries from the analytical run. The reason is that the electronic records in a CDS contain much more information than the corresponding paper printouts of the same chromatographic run.

Paper as raw data from a laboratory computerized system has now joined the dodo as extinct.

Chromatography Data System Use: Hybrid or Electronic?

If we have the FDA stating that the primary records or raw data in a CDS are the electronic records how best should the system be operated? Here, we have two choices either as a hybrid (handwritten signatures appended to paper printouts of the electronic records) or electronic (electronic signatures to electronic records). In Europe, these two options are called heterogeneous and homogeneous in EU GMP Chapter 4 on documentation,[12] for obvious reasons, we will stay with the hybrid and electronic terminology.

The simple answer, from my perspective, is to choose the electronic option. This is for a number of reasons. The first is that there is only one medium to manage — electronic records. All linkages between the chromatographic files, methods used to control the chromatograph and acquire then process the data, perform the final calculations for the reportable value and then sign the report are managed within a single system. There is also an audit trail to identify who did what and when and why.

In contrast, with a hybrid CDS, there are two types of media to manage: signed paper printouts in the physical world and the electronic records in the CDS. Plus, we must ensure that the synchronization between the two media is correct; file names used are included on the printout to provide a link to the underlying electronic records in the CDS. In the event of a deviation or complaint that may result in the data being reprocessed and new values calculated, the two sets of printouts and all the electronic records need to be managed. A hybrid system is the worst of both worlds due to this factor alone.

Regardless of the way a CDS is used, it is imperative that all the electronic records are protected from deletion or unauthorized modification by any individuals. This requires that the hardware used to run the application and store the data needs to be secure and resilient and fault-tolerant and that effective backup and recovery procedures are available and are tested and / or validated.

FDA Inspector Training in Data Integrity

As noted above, due to increased fraud detection by the agency and the issue of CPG 7346.832,9 all FDA inspectors have now undergone training in data integrity given by Monica Cahilly (Green Mountain Quality Assurance). Instead of looking at paper printouts, the focus moves to the electronic records contained within the CDS. Now, during inspections, they will focus on the system and ask somebody to take them through the analysis and audit trails rather than wrestle with the paper outputs. Paper is now incidental to the integrity of the underlying electronic records generated by any laboratory computerized system used in

Observation	Detail
Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).	• For example, your firm did not retain any raw data related to sample weights and sample solution preparations for the HPLC assays of <redacted> tablet batches <redacted> and <redacted>. that you conducted on July 18, 2012. In addition, you did not include those results in the calculation of the final assay values. Instead, you repeated the analysis the next day using a new set of sample solutions, and reported the retest results on the certificates of analysis (COAs). • Additionally, during an audit of the data submitted in support of the <redacted> regarding <redacted> tablets USP <redacted> mg, our investigator requested to review the electronic analytical raw data to compare the values for <redacted> assay and degradation products. However, your firm provided only the printed copies of the raw data because your firm did not have the software program available to view the electronic raw data.

Table 1: RPG LIfe Sciences Warning Letter Citing Lack of Complete Data[13]

Table 1: RPG LIfe Sciences Warning Letter Citing Lack of Complete Data1

a regulated laboratory. Note that complete data also includes the audit trail entries created during the generation, interpretation and modification that occur during an analysis.

So, when you get an inspection, do not be surprised if an Inspector asks somebody to show them the electronic records associated with an analysis rather than wade through reams of signed paper printouts. The electronic records are the raw data, and they will be looking to see if there are any discrepancies between that shown on the screen and what is written on paper. It is a changing regulatory world as we shall see in the next two sections by looking at what happens when you get it wrong.

Observation	Detail
Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).	• For example, you analyzed <redacted> API lot <redacted> on February 14, 2011, at 2:55 a.m., and then retested it at 2:05 p.m. using a new sample solution. You did not maintain any raw data associated with the initial test. • In your response, you stated that the retest was performed due to data deletion of the original analysis. You concluded that the analyst misused the administrator password to delete and overwrite the actual data logged in the audit trail. The ability of your analysts to alter and delete electronic analytical data raises serious concerns regarding laboratory controls in place at your facility. • During the inspection, our investigator also identified a backdated QC worksheet in the analytical report of <redacted> API raw material batch <redacted>. When your analyst affixed the related substance and IR weight printouts to the Format for Blank Sheet for Printout (Format No. F2/QCD/F/026-00), he signed and dated this worksheet as July 29, 2011. A second analyst, who reviewed this worksheet, also signed and dated it as July 29, 2011. However, your QA department did not issue this worksheet until July 31, 2011. Your analyst acknowledged during the inspection that he backdated this worksheet on July 31, 2011.

Table 2: RPG Life Sciences Warning Letter Citing Lack of Document Controls and Deletion of Failing Results[13]

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Data Integrity Citations in a Warning Letter

It can be said that the sole purpose of some organizations is to be an example to others of what not to do. A very recent warning letter was issued to RPG Life Sciences Ltd by the FDA in May 2013,[13] where there are several issues concerning data integrity and complete data. In essence, the QC Department of the company was testing into compliance by disguising non-passing analyses as "test" runs, failing to keep some electronic records and, often, when they did store the e-records — they deleted the ones that they did not like!

One of the citations for lack of complete data is shown in Table 1 where there were no records of sample weights or raw data available, and there was no program available to review the electronic raw data. This is not going to put any inspector in a good frame of mind, especially if the only (very poor) excuse for not being able to review the electronic files is because you do not have the program available. This lies is in the region somewhere between farce and utter stupidity; however, as we shall see in the next two tables, the inspection went downhill from here.

Observation	Detail
Your firm failed to establish and exercise adequate controls over computers to prevent unauthorized access or changes to electronic data.	• For example, the computers that control your analytical laboratory instruments, including an HPLC, <redacted> GCs, and an FTIR, lacked control mechanisms to prevent unauthorized access to, changes to, or omission of data files. • Your analysis of <redacted> USP batch <redacted> exceeded the <redacted> residual solvent limit on February 29, 2012. Your firm did not report or investigate this OOS result, and deleted the related electronic records. During our inspection, your analyst admitted that he also deleted other uninvestigated failing and/or OOS electronic data from the laboratory database in January 2013 prior to our inspection. Your QC Senior Manager also acknowledged this laboratory-wide electronic data deletion practice. • During our inspection, your analysts demonstrated to our investigators that they could delete any electronic analytical data files from the laboratory computers and external backup hard drives.

Table 3: RPG LIfe Sciences Warning Letter Citing Lack of Control over Computer Systems[13]

Table 3: RPG LIfe Sciences Warning Letter Citing Lack of Control over Computer Systems

You may remember at the start of this paper that one of the issues surrounding complete data was selection of passing results versus those that failed. This was reiterated with CPG 7346.832 as one of the things for which an inspector should be on their guard. Table 2 shows the problem with an analysis that was noted by the inspector in that there were two attempts at analysing a sample; the first run, which probably failed and the raw data were deleted from the system, and a second passing run where the data were retained. To compound the problem, the analyst altered the audit trail, which means that the data system did not meet 11.10(e) requirements for an audit trail.[11] To cap it all, there was a laboratory worksheet that was backdated by the analyst in collusion with their supervisor.

Things cannot get worse, can they?

Unfortunately, they can as we can see in Table 3.

If you really want to impress an FDA inspector, I would suggest that you do not do it by showing them the real-time deletion of laboratory data for batch release. Unfortunately, as shown in Table 3, the analysts from RPG's QC laboratory ignored this advice and showed the inspector their ability to delete virtually anything. Even if the laboratory systems would allow this, and many file-based laboratory systems have this ability for a user to access and delete files via the operating system, there should be procedural controls and training to stop analysts from being able to do this. Better still, the data should be acquired directly to a networked drive that is restricted or write protected or use the operating system to have a basic level of basic security.

As the FDA noted at the end of the warning letter: You are responsible for the accuracy and integrity of the data generated by your firm. A firm must maintain all raw data generated during each test, including graphs, charts, and spectra from laboratory instrumentation. These records should be properly identified to demonstrate that each released batch was tested and met release specifications.[13]

Now, you should be convinced that electronic records are the raw data and not the paper printouts from a CDS or any laboratory computerized system.

References

1. www.thefreedictionary.com/integrity (accessed July 2013)
2. ICH Q10 Pharmaceutical Quality Systems (2008)
3. Current Good Manufacturing Practice regulations for finished pharmaceutical products, 21 CFR 211 (2008)
4. Electronic records; electronic signatures final rule, 21 CFR 11 (1997)
5. United States Pharmacopoeia, United States Pharmcopeia Inc, Rockville, MD

6. Xian Libang Pharmaceutical Co., Ltd, Warning Letter, January 2010
7. Able Laboratories 483 Observations, 6 July 2005
8. R.D.McDowall, Quality Assurance Journal, 10 (2006)15-20
9. Compliance Program Guide 7346.832 Pre-Approval Inspections, FDA May 2010, effective May 2012
10. Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Records and Reports. Part 3 (2010) www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/Guidances/ucm124787.htm (accessed July 2013)
11. Part 11 Scope and Application, FDA Guidance for industry, September 2003
12. EU GMP Chapter 4 on Documentation, June 2011
13. RPG Life Sciences Ltd, Warning Letter, May 2013

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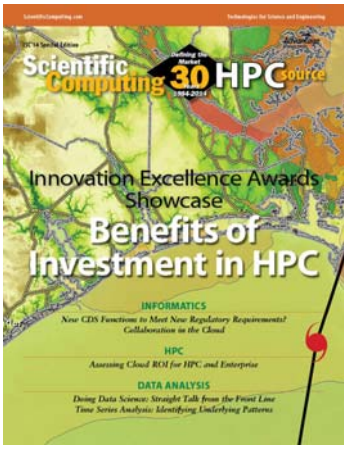

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